Tetrahedron Letters 52 (2011) 6805–6808

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

$InCl_3$-catalyzed four-component reaction: a novel synthesis of *N*-carbazolyl dihydropyridines

Ezhumalai Yamuna [a], Matthias Zeller [b], Karnam Jayarampillai Rajendra Prasad [a,*]

[a] Department of Chemistry, Bharathiar University, Coimbatore 641 046, India
[b] Department of Chemistry, Youngstown State University, One University Plaza, Youngstown, OH 44555, USA

ARTICLE INFO

Article history:
Received 3 June 2011
Revised 7 October 2011
Accepted 9 October 2011
Available online 15 October 2011

Keywords:
N-Carbazolyldihydropyridines
1,4-Dipolar addition
$InCl_3$
Four-component reaction

ABSTRACT

We have developed a simple, efficient, and environmentally benign microwave-assisted $InCl_3$-catalyzed synthesis of *N*-carbazolyldihydropyridines via a four-component reaction of 3-amino-9-ethylcarbazole, malononitrile, aromatic aldehydes, and acetylenic esters. The use of microwave heating allowed for reduced reaction times and resulted in higher yields. This four-component reaction is atom-efficient, high-yielding, and applicable to a wide variety of four-component reactions.

Multi-component, one-pot syntheses have received considerable attention because of their wide range of applications in pharmaceutical chemistry for the creation of structural diversity and combinatorial libraries for drug discovery.[1] DHPs (dihydropyridines) are an important class of compounds in the field of pharmaceuticals due to the high level of biological activity including vasodilation, bronchodilation, hepatoprotection, geroprotection, and as antiatherosclerosis, antidiabetes, antitumor, antimutagenic, antioxidant, anticonvulsant, and antiradical agents.[2] Also, 1,4-DHPs are the most potent calcium antagonists or calcium channel blockers.[3] Carbazoles and related compounds, on the other hand, also display a range of biological activities which have made them attractive compounds for both synthetic as well as medicinal chemists.[4,5] It is with that background in mind that we decided to extend the preparative scope of our synthesis of DHPs to include heterocyclic compounds such as carbazoles with DHP's building blocks in order to modify and potentially enhance their biological activities.

In the Huisgen 1,4-dipolar addition, a reactive intermediate is formed in situ by the addition of nitrogen heterocycles to electron deficient alkynes, and the reaction with different dipolarophilic reagents leads to a considerable number of heterocyclic compounds.[6] In the past years, extensive interest has been given to these 1,4-dipoles, and a number of carbon–carbon bond formation reactions and heterocyclic constructions have been established.[7] Recently, these potential 1,4-dipoles have been also widely used in multicomponent reactions to develop more atom-economic and environmentally synthetic methods. A series of three-component and four-component reactions involving nitrogen heterocycles, activated acetylenes, and electrophiles or dipolarophiles have been developed by several research groups.[8–11] Recently, this protocol has been broadened to employ primary and secondary amines to replace nitrogen heterocycles to generate the 1,4-dipolar intermediates.[12] Multi-component reactions containing a primary amine, acetylenedicarboxylate, and a third component as well as others provide new elegant procedures for the clean synthesis of polysubstituted heterocycles.[13]

Recently, indium trichloride has evolved as a mild and water-tolerant Lewis acid imparting high regio-, chemo-, and diastereoselectivity in various organic transformations.[14] Compared to conven tional Lewis acids, indium trichloride in particular has the advantages of low catalyst loading, moisture stability, and catalyst recycling. Furthermore, it is highly efficient to activate nitrogen-containing compounds, such as imines and hydrazones, etc.[15] In this Letter, we wish to report an efficient and versatile method for the $InCl_3$-catalyzed synthesis of polysubstituted *N*-carbazolyl-1,4-dihydropyridines via a four-component reaction of aminocarbazoles, aromatic aldehydes, malononitrile, and acetylenic esters.

In our initial approach, we investigated the reaction of 3-amino-9-ethylcarbazole 1,4-methoxy benzaldehyde, and malononitrile with dimethyl acetylene dicarboxylate (DMAD) in the presence of various catalysts using same solvent system at varying temperatures in a Biotage microwave oven to yield *N*-carbazolyl dihydropyridine (**5**).[16] Using as the catalyst either triethyl amine (1 mmol), piperidine (1 mmol), tin(II) chloride (1 mmol), zinc chloride (1 mmol), or ceric ammonium nitrate (1 mmol) (Table 1, entries

* Corresponding author. Tel.: +91 422 2422311; fax: +91 422 2422387.
E-mail address: prasad_125@yahoo.com (K.J. Rajendra Prasad).

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doi:10.1016/j.tetlet.2011.10.044

1–6) gave only low to moderate yields. Ytterbium triflate (1 mmol), L-proline (1 mmol), or indium(III) chloride, (entries 7–12), on the other hand, showed promising results. Ytterbium triflate or L-proline as the catalysts facilitated the formation of dihydropyridine (**5**) in good yields (around 60%). With $InCl_3$ as the catalyst the reactions proceeded smoothly in an even shorter reaction time with similar good yields, thus indicating $InCl_3$ as the most efficient catalyst of those tested (Table 1). In order to optimize the reaction conditions we evaluated the most appropriate catalyst loading. With the use of 10, 15, 20, and 25 mol % of $InCl_3$ at 70 °C the yields steadily increased with loading until it reached a maximum of >90% at 25 mol % catalyst. No additional increase in yield was observed upon further increasing the load of $InCl_3$. As seen in entries 2 and 3 (base condition), and entry 8 (amino acid), although these additives are not Lewis acids, yet the reaction proceeded smoothly to generate 1,4-dipolar intermediates. Hence, the products have been obtained in reasonable yield.

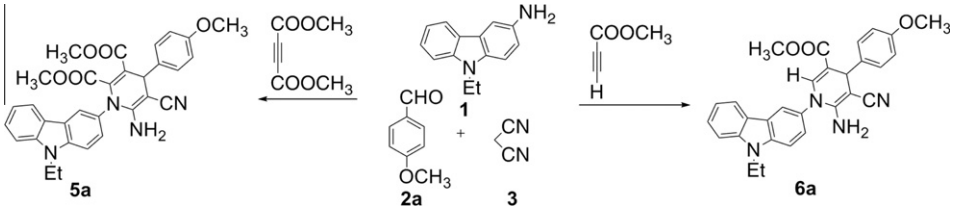
With the optimized conditions in hand, we turned our attention to examine the scope of the reaction. At first, various aromatic aldehydes were employed, and the reaction proceeded very well to give the corresponding polysubstituted *N*-carbazolyl-dihydropyridines **5a–g** in good yields as shown in Scheme 1. Dimethyl acetylenedicarboxylate also showed very high reactivity. These results indicated that this four-component reaction is quite general and has very broad substrate scopes. All compounds were isolated by crystallization only and no chromatographic work-up was required to obtain pure products. The structures of the product *N*-carbazolyl dihydropyridines **5a–g** were deduced from their elemental analysis data, and from their IR, mass, ^{1}H NMR, ^{13}C NMR spectra and one of the products was also confirmed by single crystal X-ray diffraction study. The IR spectrum of **5a**, for example, shows absorption peaks at 3442, 3317, 2184, 1745, and 1711 cm^{-1}, which attest to the presence of amino, cyano, and ester groups, respectively. ^{1}H NMR spectrum of **5a** exhibited a 2-amino group singlet δ 5.61 and the proton at the 4-position of the dihydropyridine appears at δ 4.48. Finally, the structure of one of the members of the series, **5e**, was confirmed by single crystal X-ray analysis (Fig. 1).

To extend the utility of this domino reaction, the reactivity of methyl propiolate (instead of DMAD) was also explored. Under similar reaction conditions, the four-component reaction of 3-amino-9-ethylcarbazole **1**, aromatic aldehydes, malononitrile, and methyl propiolate proceeded smoothly and regioselectively to give another series of polysubstituted *N*-carbazolyl-dihydropyridines **6a–g** in good yield as shown in Scheme 1. For compound **6a** the IR spectrum showed an unusually low frequency for the ester carbonyl group of 1701 cm^{-1}. The other IR frequencies of **6a** at 3452, 3365 cm^{-1} for NH_2 and at 2189 cm^{-1} for the cyano group were again as expected. In particular, the regiochemistry proposed for the product **6a** was decided on the basis of its ^{1}H NMR spectrum exhibiting singlets at δ 4.43 and 7.34 due to the 4- and 6-position protons of the dihydropyridine ring system. The 2-amino protons of dihydropyridine show a broad singlet at δ 5.59. This result showed that a domino reaction for the efficient synthesis of the versatile functionalized *N*-carbazolyl dihydropyridines has been successfully established. Based on specific rotation of DHP derivatives, all the compounds were found to be racemic mixtures.

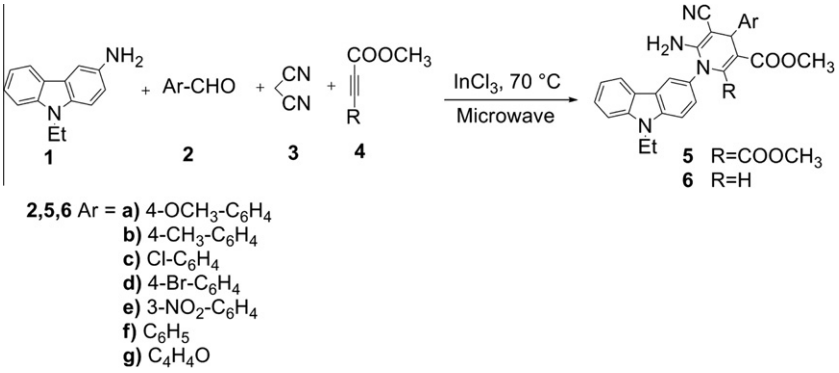
To explain the mechanism of this multicomponent reaction, we propose the following reaction course (Scheme 2). $InCl_3$-assisted Knoevenagel condensation of the aldehyde with malononitrile yields arylidene malononitrile (**A**). Arylamine added to acetylenedicarboxylate to furnish the 1,4-dipole intermediate (**B**). Then, Michael addition of **B** to arylidene malononitrile **A** yielded the adduct **C**, which transformed to intermediate **D** through the migration of the hydrogen atom. In intermediate **D**, the intramolecular addition of the amino group facilitated by $InCl_3$ to the C–N triple bond gives the cyclic intermediate (**E**). In the final step, *N*-carbazolyl dihydropyridine **5** or **6** is formed by tautomerization of the imino group to form the amino group as shown in Scheme 2.

In conclusion we have developed a novel domino four-component synthesis of dihydropyridines from the simple synthons aminocarbazole, aromatic aldehydes, malononitrile, and acetylenic esters. The remarkable catalytic activity of $InCl_3$ is superior to the other reported catalysts with respect to improved yields and reduced reaction times. The higher yields, mild reaction conditions, the ease of purification, and economic availability of the synthons

Table 1
Reaction of 3-amino-9-ethylcarbazole with *p*-methoxybenzaldehyde, malononitrile, and acetylenic esters under various conditions



Entry	Additive	Solvent	Temperature (°C)	Time (min)	Yield	
					5a	**6a**
1	—	CH_3CN	70	75	20	15
2	Et_3N	CH_3CN	70	40	45	26
3	Piperidine	CH_3CN	70	40	40	29
4	$SnCl_2{\cdot}H_2O$	CH_3CN	70	25	56	35
5	$ZnCl_2$	CH_3CN	70	30	54	38
6	CAN	CH_3CN	70	25	55	52
7	$Yb(OTf)_3$	CH_3CN	70	20	62	53
8	L-Proline	CH_3CN	70	25	66	62
9	$InCl_3$ (10 mol %)	CH_3CN	70	15	80	79
10	$InCl_3$ (15 mol %)	CH_3CN	75	15	80	79
11	$InCl_3$ (20 mol %)	CH_3CN	70	15	85	81
12	$InCl_3$ (25 mol %)	CH_3CN	70	10	93	91



Scheme 1. Synthesis of *N*-carbazolyldihydropyridines catalyzed by $InCl_3$

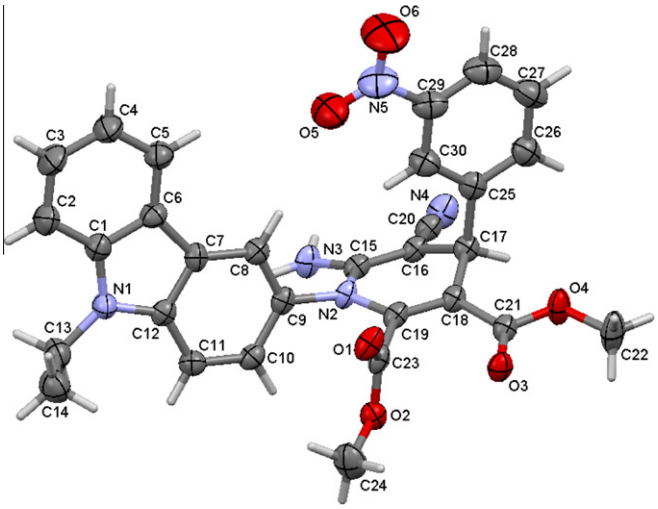


Figure 1. X-ray crystal structure of compound **5e**.

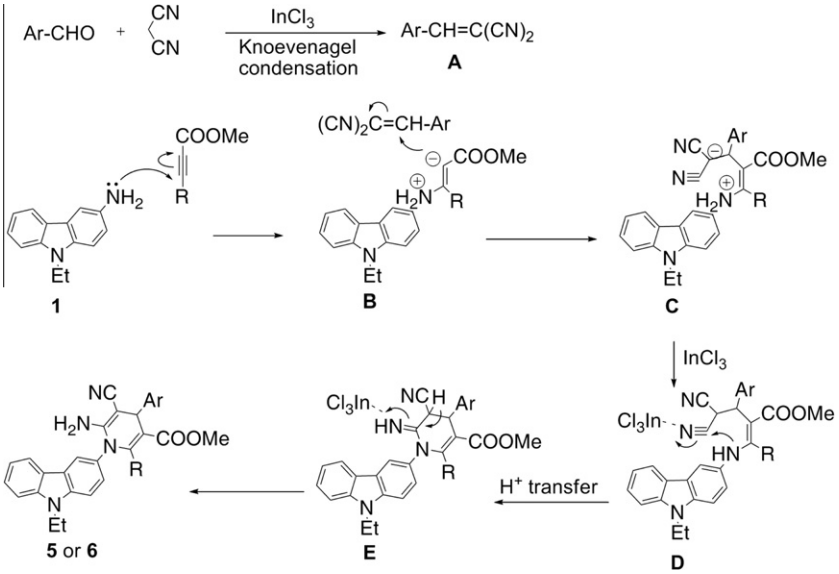
and catalyst make this an ecologically friendly procedure for the synthesis of dihydropyridines. This protocol does not only provide a novel and effective methodology for the preparation of functionalized dihydropyridines but also opens up a new pathway for employing 1,4-dipole intermediates to design other similar multi-component reactions. Further expansion of the reaction scope and synthetic applications of this methodology are in progress in our laboratory.

Acknowledgements

Our sincere thanks go to the Director, ISO Quality Assurance Cell, IICT, Hyderabad, SAIF, IIT Madras, Chennai, IISc, Bangalore and the Madurai Kamaraj University, Madurai for providing access to their Mass, NMR spectral facilities, optical rotations measurements. The diffractometer was funded by NSF grant 0087210, by the Ohio Board of Regents grant CAP-491, and by Youngstown State University.

Supplementary data

A complete cif file for compound **5e** has been deposited with the Cambridge Crystallographic Data Centre, CCDC Deposit # 819925. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.044.



Scheme 2. Mechanism for the formation of *N*-carbazolyldihydropyridines.

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16. *General procedure for the preparation of N-carbazolyl-1,4-dihydropyridines (**5** and **6**)*: A mixture of 3-amino-9-ethylcarbazole (**1**, 1 mmol), aromatic aldehyde (**2**, 1 mmol), malononitrile (**3**, 1 mmol), acetylenic ester (dimethyl acetylene dicarboxylate or methyl propiolate) (**4**, 1 mmol), and $InCl_3$ (25 mol %) was dissolved in CH_3CN and subjected to microwave irradiation (Biotage microwave oven, 70 °C, 2 bar pressure) for 10 min. The progress of the reaction was monitored by thin-layer chromatography. Upon cooling, the product precipitated from the reaction mixture, which was filtered, dried, and recrystallized from ethanol.
*Dimethyl 6-amino-5-cyano-1-(9-ethyl-9H-carbazol-3-yl)-4-(4-methoxyphenyl)-1,4-dihydro pyridine-2,3-dicarboxylate (**5a**)*: Yellow solid (0.498 g, 93%); mp: 289 °C; $[\alpha]_D^{25}$ = 0.400° ($CHCl_3$); IR (KBr) 3442, 3317, 2184, 1745, 1711 cm^{-1}; ^1H NMR (500 MHz, DMSO): δ (ppm) 1.35 (t, 3H, J = 7.0 Hz, N9-CH_2CH_3), 3.25 (s, 3H, 6′-OCH_3), 3.54 (s, 3H, 5′-OCH_3), 3.79 (s, 3H, 4″-OCH_3), 4.48 (s,1H, 4′-H), 4.50 (q, 2H, J = 7.0 Hz, N9-CH_2), 5.61 (s, 2H, 2′-NH_2), 7.02 (d, 2H, J = 8.5 Hz, 3″-H & 5″-H), 7.27 (t, 1H, J = 7.5 Hz, 6-H), 7.31 (d, 2H, J = 8.5 Hz, 2″-H & 6″-H), 7.32 (dd, 1H, J_o = 7.5 Hz, J_m = 2.0 Hz, 2-H), 7.53 (t, 1H, J = 7.5 Hz, 7-H), 7.68 (d, 1H, J = 7.5 Hz, 1-H), 7.72 (d, 1H, J = 7.5 Hz, 8-H), 8.15 (d, 1H, J = 2.0 Hz, 4-H), 8.28 (d, 1H, J = 7.5 Hz, 5-H); ^{13}C NMR (125 MHz, DMSO) δ (ppm) 14.22, 37.70, 38.40, 52.28, 52.66, 55.55, 59.99, 104.58, 109.99, 110.13, 114.63, 119.82, 121.45, 121.71, 122.33, 122.89, 122.93, 126.57, 127.00, 127.51, 128.41, 138.47, 140.02, 140.69, 142.76, 151.77, 158.74, 163.58, 165.76; MS, m/z (%): 536 (M^+, 100), 505 (38), 477 (81), 474 (21), 418 (78), 312 (18); Anal. Calcd for $C_{31}H_{28}N_4O_5$: C, 69.39; H, 5.26; N, 10.44. Found: C, 69.43; H, 5.31; N, 10.49.
*Methyl 6-amino-5-cyano-1-(9-ethyl-9H-carbazol-3-yl)-4-(4-methoxyphenyl)-1,4-dihydro pyridine-3-carboxylate (**6a**)*: Yellow solid (0.434 g, 91%); mp: 280 °C; $[\alpha]_D^{25}$ = 0.600° ($CHCl_3$); IR (KBr) 3452, 3365, 2936, 2189, 1701 cm^{-1}; ^1H NMR (500 MHz, DMSO): δ (ppm) 1.35 (t, 3H, J = 7.0 Hz, N9-CH_2CH_3), 3.52 (s, 3H, 5′-OCH_3), 3.77 (s, 3H, 4″-OCH_3), 4.43 (s,1H, 4′-H), 4.51 (q, 2H, J = 7.0 Hz, N9-CH_2), 5.59 (s, 2H, 2′-NH_2), 6.94 (d, 2H, J = 8.0 Hz, 3″-H & 5″-H), 7.26 (t, 1H, J = 7.5 Hz, 6-H), 7.28 (d, 2H, J = 8.0 Hz, 2″-H & 6″-H), 7.34 (s, 1H, 6′-H), 7.47 (dd, 1H, J_o = 7.5 Hz, J_m = 2.0 Hz, 2-H), 7.52 (t, 1H, J = 7.5 Hz, 7-H), 7.68 (d, 1H, J = 7.5 Hz, 1-H), 7.76 (d, 1H, J = 7.5 Hz, 8-H), 8.29 (d, 1H, J = 7.5 Hz, 5-H), 8.31 (d, 1H, J = 2.0 Hz, 4-H); ^{13}C NMR (125 MHz, DMSO) δ (ppm) 14.23, 37.65, 39.03, 51.57, 55.50, 60.13, 106.42, 109.92, 110.68, 114.30, 119.67, 120.63, 121.49, 122.18, 122.42, 123.38, 125.54, 126.93, 128.64, 130.90, 139.17, 139.62, 139.92, 140.71, 151.43, 158.50, 166.61; MS, m/z (%): 478 (M^+, 100), 447 (35), 419 (88), 371 (15); Anal. Calcd for $C_{29}H_{26}N_4O_3$: C, 72.79; H, 5.48; N, 11.71 Found: C, 72.74; H, 5.42; N, 11.75.